REMARKS/ARGUMENTS

Claim 74 has been amended merely to clarify that the tissue being transformed is plant tissue. The amendment does not contain new matter. Claims 74-90 are pending in the application. Entry of the amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Written description

Claims 74-90 remain rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

The Examiner states that, though Applicants claim polynucleotides encoding enzymes that enhance conversion of galactose to UDP-glucose, Applicants do not adequately describe the nucleotides or methods of their use. Applicants respectfully traverse this rejection.

The standard for determining whether an application complies with the written description requirements of 35 U.S.C. 112, first paragraph, is whether one of ordinary skill in the art recognizes from reading the disclosure, that the inventors were in possession of the claimed subject matter as of the filing date. Additionally, "a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption." MPEP 2163.04.

As stated in the previous Response, the identity of enzymes that convert galactose to UDP-glucose, and of the nucleotide molecules that encode them, are well known in the art (page 47, lines 10-11 of the specification). Applicants' disclosure provides the official Enzyme Commission classification numbers for each of the four enzymes disclosed as useful in the invention, thereby allowing one of skill in the art to immediately ascertain the identity of the enzyme and of its amino acid sequence via public databases. Applicants submit this information can readily be used to determine the identity of nucleotide molecules that can encode these enzymes.

In response to these arguments, the Examiner asserts that the specification does not disclose the sequence identity of a sufficient number of sequences of each of the broadly claimed genera of polynucleotides that convert galactose to UDP-glucose. Applicants respectfully disagree.

Applicants need not explicitly describe each and every species of a claimed genus to meet the written description requirement. Applicants need only specifically describe a representative number of species within the genus. MPEP 2163 II. A.3.(a) ii). "A 'representative number of species' means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus." *Id.*

Applicants submit that the enzymes of the galactose metabolic pathway are well-known in the art. As noted above, Applicants have identified the 4 enzymes upstream of the UDP-glucose epimerase as useful in the present invention. Applicants previously provided the Examiner with printouts from public databases providing the amino acid sequences for each of these four enzymes from *E. coli*. Applicants submit that the printouts submitted by the Applicants also disclose that sequence information for the corresponding enzymes in other species is also readily available via these databases. For example, Applicants' submitted sequence printout for *E. coli* UTP-dependent pyrophosphorylase (EC 2.7.7.10) includes 30 hyperlinks to the corresponding sequence information for the enzyme in a wide variety of species, including human, rat, mouse, and yeast. Since the nucleotide sequences encoding this limited genus of enzymes in a variety of species are readily available, Applicants respectfully submit there is no reason of record that the specification does not provide an adequate description of a representative number of species within the genus.

Furthermore, Applicants submit that methods for use of the recited polynucleotides are also adequately described. Applicants have described at least 4 different enzymes that induce conversion of galactose to UDP-glucose, and are useful in the claimed method invention. Applicants have also exemplified the transformation of cells with one such enzyme, *galT* from *E. coli*. Applicants submit there is no reason of record that transformation of a polynucleotide molecule encoding an enzyme within the recited genus, and other than *galT*, would not result in a similar insensitivity to galactose toxicity. Nor is there any reason to believe that transformation of a given enzyme in this galactose pathway (galactose to UDP-glucose) from a species other than *E. coli* would not function in a similar manner.

Furthermore, Applicants submit that it is the process steps of the present claims leading to the selection of plant cells or tissue insensitive to galactose toxicity that possess novelty and nonobviousness. Applicants do not claim polynucleotides. Rather, the claims are direted to a

novel process using known polynucleotides encoding known proteins having a known function in the galactose pathway. In process claims where: 1) the novelty is in the method steps, 2) any one of the known galactose metabolic pathway enzymes known to convert galactose to UDP-glucose can be used in the claimed invention, and 3) there is no substantial variation within the genus because there are a limited number of ways to practice the claimed process steps, the disclosure of a single embodiment (i.e. the transformation of the *galT gene*) is representative of the genus (See Example 18, Revised Interim Written Description Guidelines Training Materials). In Example 18 of the Guidelines, a claim recites a method of producing a protein comprising transforming mitochondria with an expression vector that comprises a nucleic acid encoding a protein of interest. *Id.* The novelty of the claim resided in the claimed method of expression in *Neurospora crassa*. No particular nucleic acid was essential to the claimed invention; the claim was directed to a nucleic acid encoding any protein of interest. *Id.* The specification only disclosed a single embodiment, namely, the expression of a galactosidase. *Id.* Nevertheless, the guidelines conclude that "'the single embodiment is representative of the genus based on the disclosure of neurospora crassa mitochondria as a gene expression system, considered along with the level of skill and knowledge in the gene expression art . . . [t]he claimed invention is adequately described." *Id.*

Applicants submit that the forgoing Example is applicable to the present claims. The instant claims do not require a particular polynucleotide. Any polynucleotide encoding an enzyme useful in the conversion of galactose to UDP-glucose can be used to practice the instant invention. The invention is therefore not limited to a particular polynucleotide sequence. The claims recite a novel process for selecting for transformed plant cells or plant tissue. There is no substantial variation in the recited genus, which only comprises the limited number of enzymes in the galactose metabolic pathway. Finally, Applicants have disclosed a specific embodiment (the transformation of cells with *galT*). Applicants therefore submit that the specification's specific disclosure of the transformation of plant cells with *galT*, combined with the knowledge of those of skill in the art (including the sequence information readily available from the public databases), clearly discloses embodiments that are representative of the claimed genus. Applicants submit, therefore, that the polynucleotides recited in the claims are adequately described for this additional reason.

The Examiner also argues that the public databases referred to by the Applicants are often updated or indicate a putative function, and that the information is either incorrect or subject to change. Applicants respectfully submit, however, that there is no basis in the written description requirements for rejecting claims based upon the speculation, without any concrete evidence, that the publicly available sequence of a polynucleotide falling within a recited genus of polynucleotides in the claims may contain errors. Applicants submit that a given polynucleotide sequence may contain an error regardless of whether the sequence is disclosed in a public database, or in the specification of a patent application. Applicants note that the Examiner has provided no evidence that any of the sequences submitted with the previous Response are incorrect.

The Examiner also argues it is not clear that these sequences were available to the public as of the effective filing date of the application. Applicants disagree. The present application claims priority to August 11, 1998. Applicants submit that the database printouts of sequences submitted in the previous Response are all identified by their date of submission, as well as the date of the last modification. In every case, the date of the last modification to the entry was prior to Applicants' priority date.

The Examiner also cites to *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), for the proposition that the names and enzyme classification numbers provided in the specification are inadequate, because mere disclosure of an amino acid sequence does not adequately describe a nucleic acid sequence encoding that sequence. Applicants respectfully disagree. The MPEP explicitly states that:

> "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species." MPEP 2163 II. A. 3.(a) ii).

Applicants respectfully submit that *Lilly* is not applicable to the present case. In *Lilly*, the claim at issue recited a microorganism containing a human insulin cDNA. The specification provided only a general method for obtaining the human cDNA, along with the amino acid sequences of human insulin A and B chains. The court held that the specification did "not

provide a written description of the cDNA encoding human insulin, which is necessary to provide a written description of the subject matter of claim 5." *Id.* at 1405. In reaching this conclusion, the court referred to its previous holding that "a claim to a specific DNA is not made obvious by mere knowledge of a desired protein sequence and methods for generating the DNA that encodes that protein," because the redundancy of the genetic code results in a vast number of DNA sequences that can encode the desired protein. *Id.* (citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)). The court further asserted that "a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention." *Id.* (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The court concluded that, "*a fortiori*, a description that does *not* render a claimed invention obvious does not sufficiently describe that invention for purposes of §112, ¶ 1. Because the [specification at issue] provides only a general method of producing human insulin cDNA and a description of the human insulin A and B chain amino acid sequences that cDNA encodes, it does not provide a written description of human insulin cDNA." *Id.* Therefore, the *Lilly* court's finding of inadequate written description was explicitly based on the fact that the patentee claimed DNA sequences that were not rendered obvious by the specification, because the description of an amino acid sequence does not render obvious a particular DNA molecule encoding that sequence.

Applicants submit that the fact pattern of Lilly is completely different than the present case, because the instant specification does render the claimed invention obvious. The claims of Lilly were product claims to microorganisms containing the human insulin cDNA itself. The instant claims, however, are not directed to the polynucleotides themselves. Rather, the claims recite processes for selecting transformed cells or tissue involving the use of polynucleotides encoding enzymes that are useful to convert galactose to UDP-glucose. Therefore, the relevant inquiry under *Lilly* is whether the specification's disclosure renders the claimed process obvious.

Applicants submit that the present specification does render obvious the instant process claims. The specification discloses that most plant species are unable to sustain growth with galactose as the carbon source (page 44, lines 17-19). Applicants specifically demonstrate that galactose is toxic to wheat, sunflower, oil seed rape, potato, sugar beet, and peas (Example 3). Applicants specifically exemplify the transformation of plant cells or tissue with a gene encoding an enzyme in the galactose metabolic pathway (the *E. coli galT* gene). The specification

discloses that the transformation rendered the cells insensitive to galactose toxicity, and therefore provided an effective method for selecting for the transformed cells. Applicants submit, therefore, that the foregoing disclosure would clearly render obvious the present claims, which are directed to processes for selecting for transformed plant cells or plant tissue that are insensitive to galactose toxicity, due to the transformation of the cells with a polynucleotide encoding an enzyme useful to convert galactose to UDP-glucose. Since the specification clearly renders the instant claims obvious, the *Lilly* holding is not applicable to the present case.

Applicants submit that all pending claims are fully supported by the specification for at least the foregoing reasons. Withdrawal of the rejection is respectfully requested.

Enablement

Claims 74-90 remain rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification, while enabling the transformation of potato and oil seed rape cells and tissue using the *E. coli galT* gene and selection for transformed material, allegedly does not enable the transformation of all types of cells and tissues including plants, animals, or bacteria. Applicants respectfully traverse this rejection.

As an initial matter, Applicants submit that the claims do not include within their scope the transformation of cells and tissues from animals or bacteria. Rather, the claims recite transforming plant cells or tissue. Nevertheless, Applicants have amended independent claim 74 merely to clarify that the claims are directed to the transformation of plant cells and plant tissue.

The Examiner now asserts there is inadequate guidance in the specification for the identification or isolation of a multitude of non-exemplified polynucleotides encoding a multitude of non-exemplified enzymes. Applicants disagree. As discussed above with respect to the written description rejection, the nucleotide sequences of multiple polynucleotides in multiple species that encode enzymes useful to convert galactose to UDP-glucose have already been identified and isolated in the prior art. To enable the claims, Applicants need not, and preferably should not, disclose what was already well-known in the art. MPEP 2164.01. Applicants submit that these identified polynucleotides are representative of the claimed genus, and that there is no evidence of record to the contrary.

The Examiner also continues to maintain that UDP-glucose epimerase may be a rate-limiting enzyme that negates the desired selectable advantage of transformed cells. The

Examiner acknowledges that Applicants have overcome any rate limitation of endogenous plant UDP-galactose epimerase using the *E. coli galT* gene, but allegedly have not done so with any of the other claimed enzymes that have different mechanisms and different levels of activity. The Examiner contends it would require undue trial and error experimentation to test non-exemplified genes in a multitude of non-exemplified plant species for usefulness in converting galactose to UDP-glucose. Applicants respectfully disagree.

As stated in Applicants' previous response, Applicants' disclosure exemplifies the successful selection of cells transformed with UDP-glucose dependent uridyl transferase, an enzyme upstream from UDP-glucose epimerase. Therefore, endogenous plant UDP-galactose epimerase activity was clearly sufficient to render the transformed cells insensitive to galactose toxicity, such that selection for them was possible. It is the Applicants who have discovered that UDP-glucose epimerase activity is sufficient to render the claimed selection methods effective.

Applicants therefore submit that, in regard to the sufficiency of UDP-glucose epimerase activity, it is irrelevant which upstream enzyme is selected for transformation. A rate-limiting step in an enzymatic pathway is a step wherein the reaction is not limited by substrate availability, but only by the activity of the enzyme. Therefore, if a particular enzyme in a pathway is rate-limiting, alterations in substrate availability due to transformation of any of the upstream enzymes would have no effect on the reaction rate of the rate-limiting enzyme. If the rate of the rate-limiting enzyme was insufficient to result in insensitivity to galactose toxicity in transformed cells, therefore, the selection method would fail regardless of which upstream enzyme is selected for transformation. Applicants have demonstrated, however, that this is not so. Applicants have shown that transformation of cells with a polynucleotide molecule encoding *galT*, an enzyme upstream of UDP-glucose epimerase, does in fact lead to successful selection. Therefore, the activity of UDP-glucose has been fiund sufficient for successful selection regardless of which upstream enzymes are selected for transformation.

Furthermore, and as stated in the previous Response, the present claims recite "selecting transformed cells or tissue that are insensitive to galactose toxicity." Therefore, the claims exclude from their scope any transformed cells with rate limiting steps that would negate the selective advantage of the transformed gene.

In response, the Examiner cites to *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), for the proposition that the scope of the claims must bear a reasonable correlation to the scope of

enablement. Applicants submit, however, that the Examiner has provided no evidence that the claim scope is not reasonably correlated to the scope of enablement. As discussed above, Applicants have demonstrated that UDP-glucose epimerase activity is sufficient to provide successful selection of transformed cells in multiple, diverse plant species. Applicants respectfully submit that the Examiner has provided no reason to believe that low UDP-glucose epimerase activity would negate the desired selectable advantage upon transformation of any upstream enzyme.

Indeed, the Examiner has provided evidence that teaches away from the belief that UDP-glucose epimerase is rate-limiting in a manner that negates the desired selectable advantage. As discussed in the previous Response, the Dormann et al. reference cited in the last Office Action demonstrates that "the endogenous UDP-Glc epimerase activity was present in excess in the wild-type" of Arabidopsis, such that no alteration in growth rate was observed even when the activity of the epimerase was reduced by 90% from wild-type levels (page 647). Therefore, Applicants respectfully submit that the Examiner has failed to meet the initial burden of establishing a reasonable basis to question the enablement of the claims regarding this issue, as is required. MPEP 2164.04.

Applicants also disagree with the Examiner's contention that the specification fails to show that UDP-Glc epimerase activity is sufficient to provide the desired selection in non-exemplified plant species. Applicants have demonstrated that the level of UDP-glucose epimerase activity is sufficient to provide selection across widely varying plant species. Applicants have demonstrated successful selection of transformed cells in maize (Example 2), potato cells (Example 4), and oil seed rape (Example 5). These examples are notable for the diversity of species used. As discussed in the previous Response, maize plants are monocots, while oil seed rape plants are dicots. Potato is a tuber, making it even more distinct. Since Applicants have demonstrated successful selection in multiple plant species of widely varying structure and botanical classifications, it would be more predictable than not that the claimed selection process would work in other plant species within the scope of the claimed genus. Applicants submit that the Examiner has provided no evidence to the contrary, and has therefore failed to rebut the presumption of enablement. MPEP 2164.04.

The Examiner also cites to *Rasco-Gaunt S.* et al. for the proposition that screening for plants that escape the selection process is unpredictable and requires further experimentation to

determine the best conditions of selection for each and every variety or species claimed, and when the optimal time for selection should occur in order to recover transformed material. The Examiner contends the claims are non-enabled for this additional reason. Applicants disagree.

As an initial matter, the present claims nowhere require the use of the best possible conditions of selection. "When a compound or composition claim is limited by a particular use, enablement of that claim should be based on that limitation." MPEP 2164.01(c). The present claims recite the use of a transformation process to select transformed cells or tissue that are insensitive to galactose toxicity. Therefore, while the disclosure must enable this use, Applicants are not required to optimize the steps of the invention, i.e. determine the best conditions of selection for every variety or species, and the optimal time for selection, as asserted by the Examiner. Applicants respectfully submit that the Examiner's rejection is not consistent with the standards of enablement provided by the MPEP.

Applicants further submit that *Rasco-Gaunt* et al. nowhere indicates that the present claims are non-enabled. The quantity of experimentation necessary to practice the claimed invention is only one factor in whether the experimentation is "undue." MPEP 2164.06. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *Id.* (quoting *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977). Even if the required experimentation is complex, that "does not necessarily make it undue, if the art typically engages in such experimentation." MPEP 2164.01.

The Rasco-Gaunt et al. reference discusses the transformation of a range of European wheat varieties via particle bombardment. The authors state that the frequency of 'escapes' varied considerably from experiment to experiment depending on the chosen conditions, but that 4 mg l^{-1} gluphosinate ammonium clearly gave the lowest value (page 873, second full paragraph). The reference further states that it "is difficult to compare the present selection efficiencies with those previously reported in wheat, as in the present procedure, selection was applied 'late,' i.e. after one or two rounds in regeneration medium in contrast to 'early,' for example, during callus induction and early stages of regeneration." *Id.*

Applicants submit, therefore, that Rasco-Gaunt et al. merely teaches that the efficiency of transformation varies according to the time of selection and the chosen experimental regimes. *Rasco-Gaunt* et al. nowhere teach that the transformation of wheat or any other species is infeasible. The reference nowhere teaches that the optimal conditions necessary for successful

transformation, or the optimal time of selection, cannot be determined through routine experimentation. Indeed, *Rasco-Gaunt* et al. itself is directed to optimizing transformation efficiencies. The reference teaches factors found to influence transformation efficiencies (Table 2), discloses the effect of optimization of procedures on the transformation of wheat (Table 3), and provides explanations for why transformation efficiencies vary from those disclosed in the prior art (page 873, first and second full paragraphs). Thus, Rasco-Gaunt et al. itself teaches away from the belief that one of skill in the art could not optimize the transformation procedures through routine experimentation. Applicants further submit that the nature of the optimization of selection procedures (such as those taught by Rasco-Gaunt et al.), are routine in the art of plant cell transformation, and do not require undue experimentation.

Applicants respectfully submit, therefore, that the examiner has provided no reasoning why undue experimentation would be required to evaluate the selection efficiency in non-exemplified plants or non-exemplified polynucleotides encoding enzymes useful to convert galactose to UDP-glucose.

Applicants respectfully submit that all of the instant claims are fully enabled, for at least the foregoing reasons. Withdrawal of the rejection is therefore requested.

Summary

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,
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